

**WHAT IS CLAIMED IS:**

1           1.       A method comprising:  
 2           generating a model of a biological system, the model comprising rules that express a  
 3           substitution of at least one symbol by at least another symbol, the symbols representing a  
 4           biological element, and at least some of the rules being expressed in a manner that enables an  
 5           inference engine to infer alternative results from the system based on an initial hypothetical  
 6           state.

1           2.       The method of claim 1 wherein one or more of the rules comprises an operator  
 2           for expressing a relationship between at least two of the biological elements, the operator  
 3           conforming to associative and commutative properties.

1           3.       The method of claim 1 wherein one or more of the rules expresses concurrent  
 2           state transitions.

1           4.       The method of claim 1 wherein at least some of the rules are not terminating.

1           5.       The method of claim 1 wherein at least one of the rules represents a feedback  
 2           or feedforward interaction between biological elements.

1           6.       The method of claim 1 wherein one or more of the rules is reflective.

1           7.       The method of claim 1 wherein one or more of the symbols representing the  
 2           biological elements is typed.

1           8.       The method of claim 7 wherein the types of symbols are organized in  
 2           hierarchical classes.

1           9.       The method of claim 8 wherein a symbol for one of the hierarchical classes is  
 2           matched by any symbol that is a member of the hierarchical class.

1           10.      The method of claim 1 wherein at least some of the rules are conditional.

1           11.     The method of claim 1, further comprising expressing the rules graphically by  
2     representing at least some of the symbols as points and at least some of rules as lines  
3     interconnecting points, each interconnected point corresponding to a symbol that is an  
4     operand of the rule.

1           12.     The method of claim 1 wherein one or more of the symbols represents a  
2     polypeptide selected from the group consisting of a protein kinase, a transcription factor, a  
3     cytokine, and a nucleotide binding protein.

1           13.     The method of claim 1 wherein one or more of the symbols represents a  
2     polypeptide selected from the group consisting of pRB, cyclins, cyclin-dependent kinases,  
3     cyclin-dependent kinase inhibitors, p53, E2F, and DP1.

1           14.     The method of claim 1 wherein one or more of the symbols represents a drug  
2     or exogenous agent.

1           15.     The method of claim 1 wherein one or more of the symbols represents post-  
2     translational modification.

1           16.     The method of claim 1 wherein the model of the biological system includes a  
2     first set of symbols representing molecules in a first cell and a second set of symbols  
3     representing molecules in a second cell.

1           17.     The method of claim 16 wherein one or more of the first set of symbols  
2     comprises the same symbols of the second set.

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1           18.     An article comprising machine-readable media having encoded thereon a  
2     model of a biological system, the model comprising rules that express a substitution of at  
3     least one symbol by at least another symbol, the symbols representing a biological element,  
4     and at least one of the rules being expressed in a manner that enables an inference engine to  
5     infer alternative results from the system based on an initial hypothetical state.

1           19.     The article of claim 18 wherein one or more of the rules comprises an operator  
2     for expressing a relationship between at least two of the biological elements, the operator  
3     conforming to associative and commutative properties.

1           20.     The article of claim 18 wherein one or more of the rules expresses concurrent  
2     state transitions.

1           21.     The article of claim 18 wherein at least some of the rules are not terminating.

1           22.     The article of claim 18 wherein at least one of the rules represents a feedback  
2     or feedforward interaction between biological elements.

1           23.     The article of claim 18 wherein one or more of the rules is reflective.

1           24.     The article of claim 18 wherein one or more of the symbols representing the  
2     biological elements is typed.

1           25.     The article of claim 24 wherein the types of symbols are organized in  
2     hierarchical classes.

1           26.     The article of claim 25 wherein a symbol for one of the hierarchical classes is  
2     matched by any symbol that is a member of the hierarchical class.

1           27.     The article of claim 18 wherein at least some of the rules are conditional.

1           28.    The article of claim 18 wherein one or more of the symbols represents a  
2 polypeptide selected from the group consisting of a protein kinase, a transcription factor, a  
3 cytokine, and a nucleotide binding protein.

1           29.    The article of claim 18 wherein one or more of the symbols represents a  
2 polypeptide selected from the group consisting of pRB, cyclins, cyclin-dependent kinases,  
3 cyclin-dependent kinase inhibitors, p53, E2F, and DP1.

1           30.    The article of claim 18 wherein one or more of the symbols represents a drug  
2 or exogenous agent.

1           31.    The article of claim 18 wherein one or more of the symbols represents post-  
2 translational modification.

1           32.    The article of claim 18 wherein the model of the biological system includes a  
2 first set of symbols representing molecules in a first cell and a second set of symbols  
3 representing molecules in a second cell.

1           33.    The article of claim 32 wherein one or more of the first set of symbols  
2 comprises the same symbols of the second set.

1           34.    A method comprising:  
2           receiving a set of symbols in an inference engine, the set representing a hypothetical  
3 initial state of a biological system, the symbols representing elements of the biological  
4 system; and  
5           processing the initial state using rules that express a substitution of at least one of the  
6 symbols by at least another symbol representing a biological element to infer alternative  
7 resultant states of the system.

1           35.    The method of claim 34 wherein the set of symbols representing the  
2 hypothetical initial state is generated from an expression profile for a biological sample.

1           36.     The method of claim 34, further comprising: parsing a profile for a biological  
2     sample into symbols; and include at least some of the symbols in the set of symbols  
3     representing a hypothetical initial state of the biological system.

1           37.     The method of claim 36 wherein the profile is a gene expression profile.

1           38.     The method of claim 36 wherein the profile is a polypeptide profile.

1           39.     The method of claim 36 wherein the biological sample is associated with a  
2     disease or disorder.

1           40.     The method of claim 39 wherein the disease or disorder is selected from the  
2     group consisting of cancer, diabetes, infection by a pathogen, inflammation, and a disease of  
3     aging.

1           41.     The method of claim 34 wherein infinite substitution chains are detected.

1           42.     The method of claim 34 wherein values of one or more of the symbols of the  
2     resultant states are displayed graphically as a wiring diagram.

1           43.     The method of claim 42 wherein the wiring diagram comprises a graph having  
2     lines interconnecting points, each line corresponding to a rule such that each interconnected  
3     point of the line corresponds to a symbol that is an operand of the rule.

1           44.     The method of claim 34, further comprising: comparing each of the alternative  
2     resultant states to one or more reference states.

1           45.     The method of claim 44 wherein the one or more reference states comprise a  
2     state associated with cell proliferation, cell quiescence, cell apoptosis, and cell  
3     differentiation.

1           46.     The method of claim 44 wherein the alternative resultant states are compared  
2     to two or more reference states, each reference state being associated with a diagnosis.

1           47.     The method of claim 44 wherein the hypothetical initial state represents a  
2     sample from a patient.

1           48.     The method of claim 34 wherein the set of symbols representing hypothetical  
2     initial state comprises a symbol representing a genetic alteration.

1           49.     The method of claim 44 wherein the one or more reference states comprise a  
2     state associated with a disease or disorder.

1           50.     The method of claim 49 wherein the disease is selected from the group  
2     consisting of cancer, diabetes, infection by a pathogen, inflammation, and a disease of aging.

1           51.     The method of claim 34 wherein one or more of the rules comprises an  
2     operator for expressing a relationship between at least two of the biological elements, the  
3     operator conforming to associative and commutative properties.

1           52.     The method of claim 34 wherein one or more of the rules expresses  
2     concurrent state transitions.

1           53.     The method of claim 34 wherein at least some of the rules are not terminating.

1           54.     The method of claim 34 wherein at least one of the rules represents a feedback  
2     or feedforward interaction between biological elements.

1           55.     The method of claim 34 wherein one or more of the rules is reflective.

1           56.     The method of claim 34 wherein one or more of the symbols representing the  
2     biological elements is typed.

1           57.     The method of claim 56 wherein the types of symbols are organized in  
2     hierarchical classes.

1           58.     The method of claim 57 wherein a symbol for one of the hierarchical classes  
2     is matched by any symbol that is a member of the hierarchical class.

1           59.     The method of claim 34 wherein at least some of the rules are conditional.

1           60.     The method of claim 34 wherein one or more of the symbols represents a  
2     polypeptide selected from the group consisting of a protein kinase, a transcription factor, a  
3     cytokine, and a nucleotide binding protein.

1           61.     The method of claim 34 wherein one or more of the symbols represents a  
2     polypeptide selected from the group consisting of pRB, cyclins, cyclin-dependent kinases,  
3     cyclin-dependent kinase inhibitors, p53, E2F, and DP1.

1           62.     The method of claim 34 wherein one or more of the symbols represents a drug  
2     or exogenous agent.

1           63.     The method of claim 34 wherein one or more of the symbols represents post-  
2     translational modification.

1           64.     The method of claim 34 wherein the model of the biological system includes a  
2     first set of symbols representing molecules in a first cell and a second set of symbols  
3     representing molecules in a second cell.

1           65.     The method of claim 64 wherein one or more of the first set of symbols  
2     comprises the same symbols of the second set.

1           66.     A method comprising:  
2           receiving a set of symbols in an inference engine, the set of symbols representing a  
3           hypothetical initial state of a biological system, the symbols representing biological elements  
4           of the system; and  
5           iteratively substituting at least one of the symbols by at least another symbol  
6           representing a biological element using rules that represent interactions between the  
7           biological elements until a terminal state is detected or until alternative resultant states are  
8           detected.

1           67.     The method of claim 66, further comprising outputting the terminal state or at  
2           least one of the alternative resultant states.

1           68.     The method of claim 66 wherein the hypothetical initial state represents a  
2           biological sample from a patient.

1           69.     The method of claim 68 wherein the biological sample is associated with a  
2           disease or disorder.

1           70.     The method of claim 69 wherein the disease or disorder is selected from the  
2           group consisting of cancer, diabetes, infection by a pathogen, inflammation, and a disease of  
3           aging.

1           71.     The method of claim 66, further comprising parsing a profile for a biological  
2           sample into symbols; and include at least some of the symbols in the set of symbols  
3           representing a hypothetical initial state of the biological system.

1           72.     The method of claim 66, further comprising: comparing each of the alternative  
2           resultant states to one or more reference states.



1           73. The method of claim 72 wherein the one or more reference states comprise a  
2 state associated with cell proliferation, cell quiescence, cell apoptosis, and cell  
3 differentiation.

1           74. The method of claim 72 wherein the alternative resultant states are compared  
2 to two or more reference states, each reference state being associated with a diagnosis.

1           75. The method of claim 66 wherein the set of symbols representing hypothetical  
2 initial state comprises a symbol representing a genetic alteration.

1           76. The method of claim 66 wherein one or more of the symbols representing the  
2 biological elements is typed.

1           77. A method comprising:  
2 receiving into an inference engine a rule set comprising rules that express a  
3 substitution of one or more of the symbols representing biological elements by at least  
4 another symbol representing a biological element; and determining a property of the rule set.

1           78. The method of claim 77 wherein the property comprises an indicator of  
2 whether the rules set is terminating.

1           79. The method of claim 77 wherein the property comprises an indicator of  
2 whether the rule set includes one or more rules expressing a feedback or feedforward  
3 interaction.

1           80. The method of claim 77 wherein the determining comprises associative-  
2 commutative matching.

1           81. The method of claim 77 further comprising generating a decision diagram.

1           82.     A method comprising:

2           receiving into an inference engine (1) at least a first and a second set of symbols  
3 wherein the first set of symbols represents a hypothetical first state of a biological system,  
4 and the second set of symbols represents a hypothetical second state of the biological system,  
5 and the symbols represent biological elements of the biological system, and (2) rules that  
6 express a substitution of one or more of the symbols representing biological elements by at  
7 least another symbol representing a biological element; and  
8           determining if one or more of the rules must be true or false for the first state to reach  
9 the second state by processing the first state using the rules.

1           83.     The method of claim 82 wherein the hypothetical first state represents a

2 hypothetical reference sample, the hypothetical second state represents a sample associated  
3 with a disease or disorder, and a rule determined to be true identifies biological elements  
4 represented by its operands as drug targets.

1           84.     The method of claim 82, further comprising

2 identifying a first profile for a first sample associated with the hypothetical first state  
3 of the biological system,

4 identifying a second profile for a second sample associated with the hypothetical  
5 second state of the biological system; and

6 parsing the first and second profiles to produce the first and a second set of symbols.

1           85.     The method of claim 84 wherein the first and second samples have one or

2 more genetic alterations with respect to one another.

1           86.     The method of claim 84 in which the first and second profiles include

2 information about mRNA expression.

1           87.     The method of claim 84 in which the first and second profiles include

2 information about polypeptide abundance.

1           88.     The method of claim 84 in which the first and second profiles include  
2 information about polypeptide modification.

1           89.     The method of claim 84 in which the first and second profiles include  
2 information about metabolite abundance.

1           90.     The method of claim 82 in which one or more of the rules expresses  
2 concurrent state transitions.

1           91.     The method of claim 82 in which at least some of the rules are not  
2 terminating.

1           92.     The method of claim 82 in which at least one of the rules represents a  
2 feedback or feedforward interaction between biological elements.

1           93.     The method of claim 82 in which at least one or more of the symbols  
2 representing the biological elements is typed.

1           94.     The method of claim 93 in which the types of symbols are organized in  
2 hierarchical classes.

1           95.     The method of claim 82 wherein the hypothetical first state represents a  
2 hypothetical reference sample, the hypothetical second state represents a sample contacted  
3 with a drug or exogenous agent, and a rule determined to be true identifies biological  
4 elements represented by its operands as drug targets.

1           96.     An article comprising machine-readable media having encoded thereon  
2 software configured to cause the processor to:  
3           receive a set of symbols, the set representing a hypothetical initial state of a biological  
4 system, the symbols representing biological elements of the system; and  
5           iteratively substitute one or more of the symbols representing biological elements by  
6 at least another symbol representing a biological element using rules that represent

7 interactions between the biological elements until a terminal state or until alternative  
8 resultant states are detected.

1 97. The article of claim 96 wherein one or more of the rules comprises an  
2 operator for expressing a relationship between at least two of the biological elements, the  
3 operator conforming to associative and commutative properties.

1 98. The article of claim 96 wherein one or more of the rules expresses concurrent  
2 state transitions.

1 99. The article of claim 96 wherein at least some of the rules are not terminating.

1 100. The article of claim 96 wherein at least one of the rules represents a feedback  
2 or feedforward interaction between biological elements.

1 101. The article of claim 96 wherein one or more of the rules is reflective.

1 102. The article of claim 96 wherein one or more of the symbols representing the  
2 biological elements is typed.

1 103. The article of claim 102 wherein the types of symbols are organized in  
2 hierarchical classes.

1 104. The article of claim 103 wherein a symbol for one of the hierarchical classes  
2 is matched by any symbol that is a member of the hierarchical class.

1 105. The article of claim 96 wherein the software is further to cause the processor  
2 to: receive a second set of symbols for a hypothetical second state of the biological  
3 system; and compare the second set of symbols to the terminal state or to at least one of the  
4 alternative resultant states.

1 106. An article comprising machine-readable media having encoded thereon  
2 software configured to cause the processor to:

3 receive information for a first state of a biological system;  
 4 generate symbols representing biological elements of the system; and  
 5 iteratively substitute one or more of the symbols representing biological elements by  
 6 at least another symbol representing a biological element using rules that represent  
 7 interactions between the biological elements until a terminal state or until alternative  
 8 resultant states are detected.

1 107. The article of claim 106 wherein one or more of the symbols representing the  
 2 biological elements is typed.

1 108. The article of claim 106 wherein the information comprises values, each value  
 2 reflecting the abundance of a biological element in the first state.

1 109. The article of claim 108 wherein generating comprises comparing each value  
 2 to a threshold parameter for the value, and generating a symbol for the biological element  
 3 whose abundance is reflected by the value if the value exceeds the threshold parameter.